REMARKS

Status of the Claims

1. Claims 26, 34, 56, 58, 60, and 63 are currently amended.
2. Claims 34-37 and 43 are withdrawn.
3. Claims 1-25, 27-33, 38, 39, 44-55, and 62 are cancelled without prejudice to filing one or more divisional applications.
4. Claims 26, 40-42, 56-61, and 63 are pending examination in this application.

Objections to the Specification

Examiner objected to the specification because it "contains an embedded hyperlink and/or other form of browser-executable code (see p. 60, ln. 8). Applicant requests that the specification be amended to delete reference to the objectionable text as described in the *Amendments to the Specification* section, *supra*.

Claim Rejections

1. Enablement Rejection—35 USC § 112

a. Claims 26, 29, 30, 39-42, 55-59, and 61-63

i. Examiners rejection based on β-Amyloid burden and clearance is moot following cancellation of Claims 29, 30, 39, 55 and 62

The Examiner rejected Claims 26, 29, 30 39-42, 55-59, and 61-63 as failing to comply with the enablement requirement. Specifically, the Examiner stated that "the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." (08/23/06 Office Action, p. 3 (citing 02/07/06 Office Action)).

Applicant has cancelled claims 29, 30, 39, 55, and 62. Applicant does not agree with the Examiner's basis for rejection of the cancelled claims. Applicant has cancelled the claims

without prejudice, however, in the interest of simplifying and expediting prosecution of the current application. As a result, the Examiner's enablement rejection for the reasons stated in the cited passages on pages four and six through eight of the present office action are now moot. Applicant specifically reserves the right to include the cancelled claims in one or more later-filed applications claiming priority to this application.

ii. The current invention is directed to early identification of β-amyloid variants in living patients, not an aid to determine a specific stage of Alzheimer's disease

As a preliminary matter, the Applicant seeks to clarify Examiner's statement that "Applicant argues that the instant invention provides an aid to determine the stage of AD." (8/23/06 Office Action, p.3). The Applicant reiterates and specifically incorporates Applicant's remarks on pages 9 through the first paragraph ending on page 11 in Applicant's *May 24, 2006 Response to Office Action.* Applicant believes that the Examiner has misconstrued the Applicant's prior comments on page 10 of the May 24th response that "[t]he teachings of the current invention aid in determining the stage of disease by allowing detection of truncated forms in early stages, *i.e.*, those preceding Stage S7." Tau pathology Stage S7 was specifically noted because dead subjects that are classified up to S7 on the same scale (as defined in Delacourte et al. (1999)) may be clinically asymptomatic of AD while living. (*See, e.g.*, Delacourte et al. (1999)). It should be stressed, however, that the measure of PHF-tau pathology is completely distinct assessment than the claimed invention. The tau pathology staging as described in Delacourte et al. (1999) can only be accomplished on dead subjects. Applicant further notes that the 1999 Delacourte et al. article is cited throughout the specification, including on page 78. A copy of the 1999 Delacourte et al. article is attached for the Examiner's convenience as Ref. C18.

The present invention relates to a method for the early detection of N-terminal truncated forms of β-amyloid in living patients, which aids in the determination of whether a mammal may be susceptible to or at risk of diseases associated with β-amyloid formation and/or aggregation such as Alzheimer's disease. Applicant's reference to "determining the stage of disease" in the above-quoted passage was intended to refer to the general progression of Alzheimer's disease, not identifying specific tau, β-Amyloid, or Alzheimer's staging in a living patient. The Applicant does not purport that the current invention allows for specific diagnosis of a patient in a particular stage of Alzheimer's or tau pathology in a living patient (*e.g.*, determining stages as defined in Delacourte et al. (1999) as S0, S1,...S10). Again, such staging can only be accomplished with dead subjects. Applicant's intent was to state that the current invention could be used to detect β-Amyloid variants at early stages of Alzheimer's pathology, including those later (pathologically-defined stages (after death) where the patients had no clinical signs of Alzheimer's disease (*i.e.*, those preceding Stage S7 on the PHF-tau pathology scale described in Delacourte et al. (1999)).

iii. The Application teaches how to detect and identify N-terminal truncated and post-translationally modified $A\beta_{42}$ variants in dead subjects and living persons with a disease associated with β-amyloid formation and/or aggregation.

The Examiner's enablement rejection for the remaining non-cancelled claims is, in part, because "Applicant fails to provide enough guidance as to enable one of skill in the art to detect any N-terminal truncated/post translationally modified β amyloid and use them as an aid to determine whether a mammal is susceptible to any disease associated with b-amyloid formation/aggregation as recited in the claims." (Office Action, p. 5). Applicant responds as follows.

First, Applicant has amended claim 26 to refer only to the $A\beta_{42}$ genus of β-amyloid variants. Applicant has demonstrated the detection of several N-terminal truncated and post-translationally modified $A\beta_{42}$ variants in Figures 2 and 3 of the Specification. These variants were detected by 2D-Electrophoresis and Western analysis. Said variants were identified using well-known mass spectroscopy techniques, the results of which are reported in Table 3. Further, N-terminal truncated $A\beta_{42}$ variants were detected in cerebrospinal fluid (CSF) from living patients. Thus, Applicant has "provid[ed] enough guidance as to enable one of skill in the art to detect any N-terminal truncated and post-translationally modified [$A\beta_{42}$ variants]." Skilled artisans will recognize that other detection and identification techniques are available for accomplishing these tasks.

Second, Applicant has shown that the claimed N-terminal truncated and post-translationally modified $A\beta_{42}$ variants comprise a significant amount of the β-amyloid plaques from the brains of both an infraclinical AD patient (Specification, Fig. 3), and a patient with full blown AD (Specification, Fig. 2 and Table 3). Applicant has also shown that the $A\beta_{42}$ species (rather than the $A\beta_{40}$ species) is the major component of early-stage amyloid plaque formation in AD (Specification, Fig. 4). Further, Applicant has demonstrated the presence of N-terminal truncated $A\beta_{42}$ peptides in the CSF of living patients with various stages of AD pathology (Specification, Table 8). Alzheimer's disease is a disease "associated with β-amyloid formation and/or aggregation," as recited in amended Claim 26. A skilled practitioner recognizes that the claimed invention relates to other diseases that result from or are characterized by β-amyloid formation and/or aggregation. Thus, Applicant's disclosure is sufficient to enable practitioner's to "use [the N-terminally truncated/post-translationally modified $A\beta_{42}$ peptides] as an aid to determine whether a mammal is susceptible to any disease associated with b-amyloid

formation/aggregation" as recited in the claims. Even in the absence of this explanation, however, Applicant believes that that Claim 42 drawn to Alzheimer's disease is not properly within Examiner's rejection for the reasons quoted in the previous sentence, as the application demonstrates the utility of the claimed invention in AD patients.

iv. Claim 60 directed to Aβ5-42 is enabled

Applicant appreciates the Examiner's assessment that claims drawn to Aβ5-42 are enabled. On page 5 of the August 23, 2006 office action, Examiner stated that, "[b]ased on the disclosure, **Applicant is enabled for detecting Aβ5-42** or Aβ2-42..." On the same page, the Examiner also stated that "Applicant has only shown that Aβ8-42 and **Aβ5-42 are relevant to AD**." Currently-amended Claim 60 reads: "The method of claim 26 wherein the susceptibility to Alzheimer's disease (AD) or the risk of developing AD is determined by detecting Aβ(5-42) in a body fluid sample obtained from the mammal." Because Claim 60 is directed only to the Aβ(5-42) variant, the Applicant agrees claim 60 is enabled for purposes of this response.

Applicant believes that Examiner inadvertently included claim 60 on page 8, where Examiner stated: "The rejection is applied to new claims 55-63." Applicant notes that Examiner specifically excluded claim 60 from rejection in the last sentence of the first paragraph of the section beginning on page 3 of the office action. Specifically, the Examiner stated: "The rejection is applied to newly added claims 55-59 and 61-63." Accordingly, it appears that Examiner's inclusion of claim 60 on page 8 of the office action was merely an oversight.

v. Claim 43 is now ready for examination and is enabled

If the Examiner finds that Claim 60 is suitable for allowance, Applicant requests that Examiner now address the merits of Claim 43, which states: "The method of claim 26 wherein the susceptibility to Alzheimer's disease (AD) or the risk of developing AD is determined by detecting Aβ(5-42) or Aβ(8-42) in a body fluid sample obtained from the mammal." Claim 43 differs from Claim 60 in that Claim 43 includes the Aβ(8-42) species. Examiner agrees that Applicant has shown that both "Aβ8-42 and Aβ5-42 are relevant to AD." (Office Action, p. 5). The Examiner's enablement rejection regarding Aβ8-42, however, is based on the following:

> The data shown in figures 4 and 7 and table 8 indicate that N-terminally truncated Aβ peptides 8-42 and 5-42 are detected in the CSF of AD patients. However, Aβ8-42 is also detected in the S0 control and so are Aβ11-42 and Aβ10-42, indicating that the presence of these forms of N-terminal truncated Aβ is a natural phenomenon.

(Office Action, p. 5). As described below and evidenced by the current specification, the detection of the $A\beta_{42}$ variants in a sample from a subject designated as 'S0" and as a "control" in the figures cited by Examiner is consistent with the claimed invention and not a "natural phenomenon."

1. Aβ42 is a unique marker related to Alzheimer's disease etiology distinct from PHF-Tau

Applicant has attached the Declaration of Dr. Eugeen Vanmechelen to assist in addressing the Examiner's concerns. As described in the Declaration, Dr. Vanmechelen is intimately familiar with the subject matter of the Application because he has collaborated with the named inventors to further develop the technology as an employee of the assignee of the pending application, Innogenetics NV. (Vanmechelen Declaration, ¶¶1-4). Dr. Vanmechelen has been asked specifically to address the Examiner's concerns stated in the block quote above reproduced

from page 5 of the Office Action (*See* Vanmechelen Declaration, ¶¶ 5-7). As described by Dr. Vanmechelen, the term "control" is used differently in different portions of the specification, and detection of N-terminal truncated Aβ peptides in subjects designated as "control" subjects is consistent with the claimed invention. Possible confusion results from the use of the term "control" as explained below.

As part of a 1999 study conducted by the named inventors (and other researchers), the patients described in Figures 4 and 7 and Table 6 were given a full clinical evaluation prior to their death. After the same patients died, PHF-tau pathology was assessed in samples taken from the subjects' brains (Id. at ¶ 8). The same subjects were also part of a 2002 study conducted, in part, by the inventors of the present application. The subjects examined in the 1999 and 2002 studies were also used to conduct the experiments described in this Application (Id. at ¶ 9). The subjects were given certain designations in the 1999 study, based only on their clinical evaluations during life, and the extent of their PHF-tau pathology staging determined after the subjects died. As the focus of the 1999 study was PHF-tau pathology staging, data regarding β-Amyloid was not used to classify the subjects (Id. at ¶ 10).

In the inventor's prior studies, the designation of a subject as "control" meant that the patients fell within one of two categories. The first category of "control" subjects included those that had no tau pathology as determined after death ("S0" subjects). The second category of subjects designated as "controls" were comprised of subjects with a PHF-tau pathology stage S1-S7 after death, but who exhibited no signs of clinical impairment in their prior clinical examination while alive. (*See* Id. at ¶ 11). Based on the results of the prior studies, the inventors proposed certain diagnostic criteria to accurately diagnose dead subjects with AD, and these diagnostic criteria have a β-Amyloid component. The authors refer to the diagnostic criteria as

"CEBDAD." The term "control" is used as part of the CEBDAD diagnostic criteria. The criteria are reproduced on page 4 of the Specification. (Vanmechelen Declaration, ¶ 12).

Although reproduced at page 4 of the Specification, the definition of "control" from the CEBDAD criteria for dead subjects is not used in Figures 4 or 7 or in Table 6 in the Specification. Thus, the uses of the term "control" as described above are not inconsistent with the present invention, because they are not based on detection of N-terminal truncated or post-translationally modified Aβ peptides as described in the Application. Further, while the prior studies involved detection of PHF-tau and total β-Amyloid, no samples were taken from living patients (Id. at ¶ 13).

To illustrate the distinction described above, Applicant directs Examiner to Figures 4 and 7 of the Specification, both of which show a subject designated as "S0." As further described in the Vanmechelen Declaration, these S0 subjects were originally described as "controls" in the 1999 Delacourte et al. publication because they had no PHF-tau protein in any part of the brain. (Id. at ¶ 14). In Figure 4 of the Specification, no $A\beta_{42}$ peptide was detected in the brain of the S0 subject. The same figure shows, however, that $A\beta_{42}$ was detected in patients with increased PHF-tau pathology. (Id. at ¶ 15). The absence of $A\beta_{42}$ in some S0 patients demonstrates that $A\beta_{42}$ is not in all people's brains, suggesting that its presence is not merely a "natural phenomenon." As described by Dr. Vanmechelen, detection of $A\beta_{42}$ variants in clinically-demented patients with tau pathology and non-demented patients with tau pathology suggests that $A\beta_{42}$ may be used as a marker for AD. (Id. at ¶ 16). The utility of N-terminal truncated $A\beta_{42}$ peptides as such markers is highlighted by the detection said peptides in preclinical AD patients such as in Figure 7 (See Id. at ¶ 17)

Unlike in Figures 4 and 7 and Table 6, the data described in Tables 7 and 8 of the Application were obtained from living patients. The patients' clinical diagnosis was based on CSF samples obtained by lumbar puncture and through other clinical evaluations (Vanmechelen Declaration, ¶ 18). Detection of N-terminal truncated $A\beta_{42}$ peptides in CSF of patients designated as "controls" is significant because it may signal that the patient is at risk of or susceptible to Alzheimer's (Id. at ¶ 19). Thus, detection of N-terminal $A\beta_{42}$ peptides in both deceased and living patients designated as "controls" is not merely a "natural phenomenon," rather it signifies that the "control" patients may be in preclinical stages of AD or another disease associated with β-amyloid formation and/or aggregation. (Vanmechelen Declaration at ¶ 20). As described in the Specification, the detection of N-terminal truncated $A\beta_{42}$ peptides provides a means both to detect preclinical AD pathology in living patients, and to more accurately diagnose diseased patients. (Id. at ¶ 21).

Applicant directs the Examiner to Appendix 3 of the Vanmechelen Declaration in further support of Applicant's explanation that there are two well-defined classes of "control" patients—some which have preclinical AD pathology and other that have no AD pathology. As described in paragraphs 22-25 of the Vanmechelen Declaration, Appendix 3 is an extension of the Delcourte et al (2002) and Deramecourt et al. (2006) studies. Appendix 3 differs from prior studies in that, in addition to PHF-tau and Aβ staging, the patient samples are assessed for the presence of specific N-terminal truncated $A\beta_{42}$ peptides. These studies further indicate that there are two different populations of "controls." Those subjects highlighted in yellow represent normal aging "controls," whereas the remainder of the "control" patients in Table 1 of Appendix 3 are likely in early stages of AD (Id. at ¶¶ 26-28). Thus, detection of N-terminal truncated $A\beta_{42}$ peptides in samples from these subjects is significant in that it signals early stages of AD. As

shown in the specification and in Appendix 3, certain $A\beta_{42}$ variants are frequently detected in subjects with infraclinical AD. (See Vanmechelen Declaration, ¶ 29) These and other N-terminal truncated $A\beta_{42}$ peptides are also detected in subjects with full blown AD. (Id. at ¶ 30). Identification of the N-terminal $A\beta_{42}$ variants in early stages of AD is significant because these variants are thought to initiate amyloid plaque formation/aggregation (Id. at ¶ 31). Determining the risk or susceptibility to AD in early stages may provide an opportunity mitigate or prevent further development of AD pathology.

Applicant believes that the foregoing explanation sufficiently addresses the Examiner's concerns regarding the presence of N-terminal truncated $A\beta_{42}$ peptides in "controls." Because the Examiner has already stated that the specification shows that "Aβ8-42 and Aβ5-42 are relevant to AD," Applicant requests that the Examiner now advance claim 43 to allowance.

2. Claim 57 drawn to elected species Aβ4-42 is enabled

As stated above, Examiner rejected, among others, Claim 57 for lack of enablement because "the data shown in the specification are derived from patients suffering from Alzeheimer's disease rather than patients who are free of Alzheimer's disease and later develop Alzheimer's disease." (8/23/06 Office Action, pp. 5-6). Applicant respectfully traverses.

As shown in the Specification and detailed in Dr. Vanmechelen's Declaration, certain N-terminal truncated $A\beta_{42}$ peptides appear frequently in infraclinical stages of AD (Id. at ¶ 29). The specification also shows detection of the $A\beta_{42}$ variants in a subject with full blown AD (Specification, Fig. 2) and a subject with infraclinical AD (Specification, Fig. 3) (*See* Id. at ¶32). As described in the Declaration, the early detection of certain species of N-terminal truncated $A\beta_{42}$ variants in infraclinical patients in Figure 3 of the Application and Appendix 3 of the

declaration has also been shown in transgenic mice models in Cases et al. (2004) (See Vanmechelen Declaration, ¶33).

Table 8 of the Specification shows the results of CSF samples taken from patients that represent a broad spectrum of AD pathology (from "control" to "Severe AD"). Specifically, the Application shows that the claimed N-terminal $A\beta_{42}$ variants are present in CSF of both infraclinical AD patients and those with Clinical AD. (Specification, Table 8). Finally, based on the disclosure in the Application, Dr. Vanmechelen and others have recently shown that there is an increased presence of N-terminal truncated$A\beta_{42}$ variants in the CSF of infraclinical AD patients that later develop into AD patients (Id. at ¶34 (*citing* Vanderstichele et al. (2005)).

In summary, Applicant has presented four different lines of evidence establishing that N-terminal truncated $A\beta_{42}$ variants are linked to AD etiology, including: (1) biochemical detection of N-terminal truncated $A\beta_{42}$ variants in both infraclinical and clinical AD patients (Specification, Figs. 2 and 3), (2) detection of N-terminal truncated $A\beta_{42}$ variants in CSF of infraclinical and clinical AD patients (Specification, Table 8); (iii) confirmation of the presence of the N-terminal $A\beta_{42}$ variants in early stages of AD-like pathology in a transgenic mouse (i.e., mammal) model (*See* Casas et al. (2004) at Fig. 3), and (iv) short-term longitudinal studies utilizing the techniques described in the specification showing that an increase in N-terminal truncated $A\beta_{42}$ variants is observed in CSF of infraclinical (MCI) patients that later develop AD. (See Vanderstichele et al. (2005)).

Applicant believes that the foregoing discussion has properly addressed the examiner's enablement rejection, which included the elected 4-42 species. Applicant respectfully requests that Claim 57 be advanced to allowance, and that Examiner continue to examination the remainder of the withdrawn claims on the merits.

2. New Matter Rejection—35 USC § 112, ¶1

Examiner rejected claims 29, 39, 40, 55, 60 and 63 for failing to comply with the written description requirement because the claims were drawn to "one or more," or "one or more particular N-terminal truncated/post-translationally modified β-amyloid variant." (8/23/2006 Office Action, pp. 8-10). Applicant has cancelled claims 29, 39 and 55 rendering the objection to those claims moot. The remaining claims (claims 40, 60 and 63) now depend from amended claim 26.

3. Indefiniteness Rejection—35 USC § 112, ¶2

Examiner has rejected claims 26, 29, 30-42, and 55-63 as being indefinite for "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (08/24/2006 Office Action, p. 10). Specifically, Examiner rejected the claims as "indefinite because the claims recite 'particular.'" *Id.* In this response, Applicant has cancelled claims 29, 30-32, 39, 55 and 62 and Claim 38 was cancelled in a prior response, rendering the objection to those claims moot. Claim 26 has been amended in this response to remove the language cited in the Examiner's rejection. Claims 33-37, 40-42, 56-61, and 63 now all depend from Claim 26. Accordingly, Applicant believes that this Indefiniteness Rejection has been overcome.

Conclusion

Applicant believes that Examiner's Objections and Rejections have been adequately addressed and overcome through amendment of the claims and the foregoing remarks. The Applicant does not believe that any other fees are due. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, the Commissioner is authorized to deduct said fees from Deposit Account No. 08-

3038/**11362.0039.NPUS01**. Reconsideration of the application is respectfully requested. Applicant respectfully requests that the claims now be advanced to allowance.

Request for Interview

Upon review of this response, Applicant requests that Examiner contact Applicant through the undersigned attorney to discuss the remaining issues pending in this case. Applicant would like to propose an interview to help resolve any outstanding issues following the Examiner's review of this response, if any. Applicant proposes that a personal interview be conducted on either June 8th or June 13th, as Dr. Eugeen Vanmelechen (the declarant to the Rule 132 Declaration attached to the response) will be traveling to Washington, DC area from Belgium for a scientific research conference scheduled for June 9-12, 2007.

Respectfully submitted,

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